PHYSICAL CHEMISTRY 2016

13th International Conference on
Fundamental and Applied Aspects of
Physical Chemistry

Proceedings
Volume I

B E L G R A D E
September 26 - 30, 2016

ISBN 978-86-82475-34-7
Title: Physical Chemistry 2016 (Proceedings)
Editors: Željko Čupić and Slobodan Anić
Published by: Society of Physical Chemists of Serbia, Studentski trg 12-16, 11158, Belgrade, Serbia.
Publisher: Society of Physical Chemists if Serbia
For Publisher: S. Anić, President of Society of Physical Chemists of Serbia
Printed by: "Jovan", Printing and Publishing Company; 200 Copies.
Number of pages: 6+502; Format B5; printing finished in September 2016

Text and Layout: "Jovan"

200 - *Copy printing*

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13th International Conference on
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Organized by

The Society of Physical Chemists of
Serbia

in co-operation with

Institute of Catalysis Bulgarian Academy of Sciences

and

Boreskov Institute of Catalysis Siberian Branch of
Russian Academy of Sciences

and

University of Belgrade, Serbia:

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DULOXETINE ENHANCES HEPATIC GSH-DEPENDENT DEFENSE IN RATS

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ABSTRACT
Duloxetine (DLX) is antidepressant for the treatment of depression, but its effect on the liver, a primary site for drug metabolism, has yet to be determined. The effect of 3 weeks of DLX treatment on protein carbonyl groups and activities of GSH-dependent defense including reduced glutathione (GSH), glutathione peroxidase (GPx) and glutathione S-transferase (GST) in liver of rats exposed to 6 weeks of chronic social isolation (CSIS), an animal model of depression, were investigated. CSIS induced increase in protein carbonyl content, which was decreased by DLX treatment. We noticed increase in GPx and GST activity in DLX-treated (controls and CSIS) rats and CSIS group, whereby GPx activity was significantly higher in DLX- compared to vehicle-treated CSIS rats. Results indicate protective effect of DLX against CSIS-induced oxidative damage of hepatic proteins, which may be due to intensified protective mechanisms mediated by GSH-dependent defense.

INTRODUCTION
It has been shown that chronic social isolation (CSIS) induced the oxidative stress in the rat liver, judged by increased concentrations of protein carbonyl groups [1]. CSIS is mild psychosocial stress used for studding pathophysiology of mood disorders [2]. A duloxetine (DLX), a selective serotonin/norepinephrine reuptake inhibitor,,is used for the treatment of some mood and nerve disorders including depression and some anxiety disorders [3].
In order to defend against oxidative stress, liver uses glutathione (GSH)-dependent defense system. Glutathione peroxidase (GPx) reduces lipid hydroperoxides to their corresponding alcohols and free hydrogen peroxide to water, using GSH as cosubstrate. Glutathione S-transferase (GST) catalyses the conjugation of the reduced form of GSH to xenobiotic substrates for the purpose of detoxification.

Since the liver possesses one of the highest antioxidant enzyme capacities in the body, and is primary organ for drug activation and detoxification, we examined the chronic effect of DLX on protein carbonyls as well as GSH-dependent defense system in liver of rats exposed to CSIS.

EXPERIMENTAL

Adult (2.5 month old) male Wistar rats were used for the experiments. Rats were housed under standard conditions (temperature-controlled environment (21-23°C), 12-h light/dark cycle with food and water available *ad libitum*). Rats were divided into control groups (four animals per cage) and rats that underwent CSIS for a period of 6 weeks, which were housed individually. After 3 weeks of experiments, rats were subdivided on groups treated either with intraperitoneal (i.p.) injections of DLX (10 mg/kg/day) (Con+DLX, CSIS+DLX) or 0.9% NaCl (Con+Veh and CSIS+Veh) for next 3 weeks. Hepatic cytosolic fractions were used for biochemical parameters determination. GPx and GST activity were determined by spectrophotometric assays [4, 5], while GSH content was measured according to Hissin and Hilf [6]. Protein carbonyl content was determined using Levine et al. method [7]. Data were analyzed by two-way ANOVA followed by Duncan's post-hoc test. The results are presented as mean ± S.E.M. of 6 animals per group.

RESULTS AND DISCUSSION

Significant increase in protein carbonyl content in CSIS+Veh group compared to Con+Veh group ($^{***}p<0.001$) (Figure 1) indicates the presence of oxidative stress. Also, it can be noticed that DLX alone probably had no effect on the liver, according unchanged protein carbonyl content in Con+DLX group compared to Con+Veh group ($p>0.05$). Chronic administration of DLX in CSIS group induced significant decrease in protein carbonyl content compared to CSIS+Veh group ($^{\hat{}\hat{}\hat{}}p<0.001$). This indicates a protective effect of DLX in relation to the changes in the proteins created by oxidative stress.

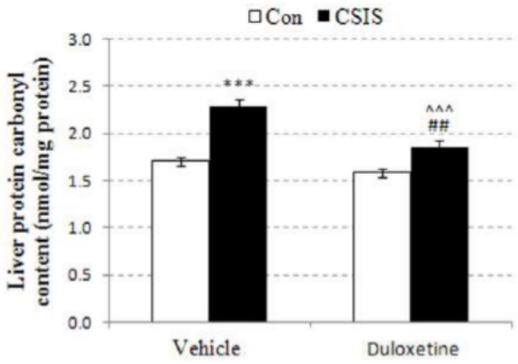

Figure 1. Cytosolic protein carbonyl contents (nmol/mg protein) in rat liver of controls and chronic social isolation (CSIS) rats treated with saline (0.9% NaCl) or duloxetine (DLX) (10 mg/kg/day). Significant differences between tested groups are indicated as follows: CSIS+Veh *vs* Con+Veh $^{***}p<0.001$; CSIS+DLX *vs* CSIS+Veh $^{\hat{}\hat{}\hat{}}p<0.001$; CSIS+DLX *vs* Con+DLX $^{\#\#}p<0.01$.

Results of hepatic GSH content and activity of GPx and GST are shown in Table 1. GSH content in CSIS+DLX group was increased compared to Con+Veh ($^{*}p<0.05$) and CSIS+Veh ($^{\hat{}}p<0.05$) groups. Unchanged GSH content in CSIS compared to control group was observed ($p>0.05$). GPx and GST activity in all treated experimental groups compared to Con+Veh group was significantly increased ($^{**}p<0.01$, $^{***}p<0.001$). Post-hoc test also showed significant increase of GPx activity in DLX-CSIS group in comparison with CSIS+Veh ($^{\hat{}\hat{}}p<0.01$) and Con+DLX ($^{\#}p<0.05$).

Table 1. GSH content, GPx and GST activity in liver of controls and chronic social isolation (CSIS) rats treated with vehicle (0.9% NaCl) or duloxetine (DLX) (10 mg/kg/day). Simbols show significant differences between: treated experimental groups and Con+Veh $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$; CSIS+DLX and CSIS+Veh $^{\hat{}}p<0.05$, $^{\hat{}\hat{}}p<0.01$; CSIS+DLX and Con+DLX $^{\#}p<0.05$.

Groups	GSH content (nmol/mg protein)	GPx activity (U/mg protein)	GST activity (U/mg protein)
Con+Veh	46.87 ± 0.72	1.37 ± 0.05	0.48 ± 0.03
Con+DLX	47.49 ± 0.84	1.82 ± 0.03 ***	0.62 ± 0.02 **
CSIS+Veh	46.89 ± 1.06	1.72 ± 0.04 ***	0.64 ± 0.03 ***
CSIS+DLX	50.16 ± 0.98 * ^	1.98 ± 0.08 *** ^^ #	0.64 ± 0.03 ***

We found that chronic DLX treatment increased antioxidant status of control and CSIS groups relative to vehicle controls. This may reveal that DLX possesses antioxidant effects in the absence of oxidative stress as well

as it directly interfere with CSIS-induced pathways of oxidative defense. Increased activity of GPx in CSIS+DLX rats may be the consequence of increased levels of GSH in these animals, since it represents a cosubstrate necessary for its activity. Moreover, increase in GPx activity, at least in part, may be responsible for reduction of protein carbonyl content in CSIS rats, suggesting protective role of DLX. Increased GST activity in DLX-treated (control or CSIS) rats, was probably due to engagement of this enzyme in the detoxification of xenobiotics, including drug..

CONCLUSION

Our data reveal that CSIS causes oxidative damage of proteins and affects the GSH-dependent defense system in the rat liver. CSIS resulted in enhanced hepatic GPx and GST activity which indicate protective effect against oxidative stress. DLX treatment increases reduced GSH and GPx activity that suggest its protective effect against CSIS-induced oxidative protein damage.

Acknowledgement

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grant no. 173044).

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CIP - Каталогизација у публикацији - Народна библиотека Србије, Београд

544(082)
66.017/.018(082)
502/504(082)
663/664:658.56(082)
615.31:547(082)

INTERNATIONAL Conference on Fundamental and Applied Aspects of Physical Chemistry (13 ; 2016 ; Beograd)
Physical Chemistry 2016 : proceedings. Vol. 2 / 13th International Conference on Fundamental and Applied Aspects of Physical Chemistry, Belgrade, 26-30 September 2016 ; [editors Željko Čupić and Slobodan Anić]. - Belgrade : Society of Physical Chemists of Serbia, 2016 (Belgrade : Jovan). - IV, 507-930 str. : ilustr. ; 24 cm

Tiraž 200. - Bibliografija uz svaki rad.

ISBN 978-86-82475-33-0

1. Society of Physical Chemists of Serbia (Beograd)
a) Физичка хемија - Зборници b) Наука о материјалима - Зборници c) Животна средина - Заштита - Зборници d) Животне намирнице - Контрола квалитета - Зборници e) Фармацеутска хемија - Зборници
COBISS.SR-ID 225802508

08. 09. 2016